Potential treatment strategy for the rare osimertinib resistant EGFR L718Q mutation

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Mutations in the epidermal growth factor receptor (*EGFR*) are one of the most important factors in determining treatment strategies for advanced lung cancer. According to the current National Comprehensive Cancer Network (NCCN) guidelines (1), osimertinib is recommended as one of the first-line options for *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC), with a median progression-free survival (PFS) of 18.9 months and median overall survival (OS) of 38.6 months (2,3), which is a remarkable progress compared to the results obtained with cytotoxic anticancer drug therapy (4,5).

The development of such molecularly targeted therapies has led to improved therapeutic efficacy; however, these effects are not permanent, and resistance to osimertinib has been observed. The most well-known example of resistance to molecularly targeted drugs is the incidence of T790M mutations, triggered by the use of a first- or second-generation *EGFR*-tyrosine kinase inhibitor (TKI). Osimertinib is a third-generation TKI, selective against both EGFR-TKI-sensitizing and T790M mutations, and has been used in patients with resistant mutations to first- or second-generation EGFR-TKIs (6-8). Current guidelines demonstrate that osimertinib should be considered as one of the first-line options for patients with *EGFR*-mutated NSCLC (1); however, there is no molecular target therapy against *EGFR*-dependent osimertinib resistance, or EGFR-independent resistance to osimertinib, mediated via the amplification of *PIK3CA*, *KRAS*, *BRAF*, *HER-2*, or *MET*.

In 2020, Song *et al.* (9) reported a case of a 44-year-old Chinese man with advanced lung adenocarcinoma, harboring the L858R mutation in EGFR. The patient had bilateral pulmonary metastases, subcarinal lymph node metastases, and pleural dissemination (cT4N2M1a-IV). As EGFR-TKIs were not being used in China then, platinum doublet (cisplatin/pemetrexed) was administered to the patient as a cytotoxic systemic chemotherapy. After four courses of platinum doublet therapy resulting in stable disease, icotinib was adopted as a molecular target therapy because it was approved for use in China as a first-line EGFR-TKI in patients with *EGFR*-mutated NSCLC (10). Initial computed tomography (CT) imaging after 4 weeks of oral administration of icotinib revealed that the main tumor in the left upper lobe and the tumor metastasized to mediastinal lymph nodes and bilateral pulmonary had undergone shrinkage. However, chest CT confirmed the regrowth of the main pulmonary tumor after a total of 32 weeks of icotinib treatment, and *EGFR* T790M mutation was detected by genetic testing with next generation sequencing (NGS)-based circulating tumor DNA (ctDNA) analysis for the first time in this case.

The patient was referred to the author's institution, and osimertinib therapy was initiated. However, no response was observed after 4 weeks of treatment, and disease progression was confirmed. As the objective response rate of osimertinib in patients with the T790M mutation after first-generation EGFR-TKI therapy is reported to be 71% (1), the expected results were not observed. To investigate the mechanisms underlying resistance to osimertinib, a pulmonary metastatic

tumor in the left lower lobe was surgically resected, and a third NGS-based testing was performed for this patient. The L718Q mutation was consequently detected along with the L858R mutation, whereas the T790M mutation was not detected. This suggested that the results of genetic mutation testing using ctDNA could be difficult, owing to false negatives caused by an inadequate volume of ctDNA in the plasma sample of the patient. Furthermore, there is a possibility of contamination with cell-free DNA from normal cells. Therefore, it is always necessary to be cautious about false positive or false negative results in ctDNA testing for genetic mutations. Therefore, an alternative genetic testing approach should be reconsidered when the expected therapeutic effect is not achieved, and the treatment may be altered if false positive or false negative results are proven.

Platinum doublet cytotoxic chemotherapy (cisplatin/ gemcitabine) was thereafter administered to the patient; however, only a partial response was observed, and the disease subsequently progressed. Diagnostic imaging revealed an increasing number of multiple pulmonary metastases, in addition to multiple brain metastases. To determine a therapeutic regimen, oncogene mutation profiling was conducted by ctDNA analysis, which surprisingly resulted in the detection of the T790M mutation yet again. The patient was rechallenged with osimertinib, and again resulting in only a partial response. This led us to enquire the rationale for the success of osimertinib rechallenge. The considerations in this regard are as follows: during the first treatment with osimertinib, most of the T790M mutant tumor cells had tumor cells did not survive, while tumor cells with other genomic types, without the T790M mutation could survive and increase in numbers. After 4 weeks of the first treatment with osimertinib, most of the surviving tumor cells did not possess the T790M mutation, which explained why the expected therapeutic effect was not achieved. Subsequent treatment with cytotoxic chemotherapy dramatically reduced the population of tumor cells that did not harbor the T790M mutation, but the primary and metastatic tumors enlarged owing to a small number of tumor cells with T790M-mutated *EGFR* that had survived covertly. Consequently, the population of tumor cells gradually increased despite treatment with cisplatin/gemcitabine. Owing to changes in the genomic profile, osimertinib rechallenge was successful and produced a therapeutic effect. Taken together, these observations suggest that it is necessary to consider the heterogeneity of the tumors while selecting the therapeutic drug, as it may affect treatment efficacy and contribute to the long-term survival of patients.

At the final stage of treatment, a C797S mutation appeared in this case in addition to the other *EGFR* mutations (L858R, L718Q, and T790M), and osimertinib was no longer effective for the patient, resulting in death. A phase 3 study using osimertinib as a second-line therapy in patients with the T790M resistant mutation (AURA3) revealed that the median OS was 26.8 months (8). Therefore, we believe that the expected therapeutic effect was observed in this case.

In summary, NGS-based detection of mutations was useful for precision medicine at the time of disease progression in this case, because it revealed the mechanism underlying drug resistance. In general, it may be difficult to perform multiple NGS-based mutation detection tests in the same patient owing to the issues of medical insurance and/or high cost. It is therefore important to understand when and how oncogene profiling should be performed in such cases, for determining the genomic status of driver mutations. The heterogeneity of tumors must be taken into account when considering the treatment strategy after second-line therapy.

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Footnote

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